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=> d his

     (FILE 'HOME' ENTERED AT 11:22:37 ON 02 MAY 2003)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 11:23:02 ON 02 MAY 2003
L1         21973 S "LDL RECEPTOR?"
L2        224249 S LOW (A) DENSITY
L3        156053 S L2 (A) LIPOPROTEIN
L4         17154 S L3 (A)RECEPTOR?
L5         30924 S L1 OR L4
L6           154 S "P42/44MAPK"
L7           154 S P42(W)44MAPK
L8           154 S L6 OR L7
L9            21 S L8 AND L5
L10           11 DUP REM L9 (10 DUPLICATES REMOVED)
                 E MEHTA K D/AU
L11          122 S E3
L12           58 S L5 AND L11
L13            4 S L7 AND L12
L14            4 DUP REM L13 (0 DUPLICATES REMOVED)
L15            4 S L8 AND L11
L16           21 DUP REM L12 (37 DUPLICATES REMOVED)
L17           13 S L16 AND MAPK
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NEWS 4	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
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NEWS 19	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 20	Feb 13	CANCERLIT is no longer being updated
NEWS 21	Feb 24	METADEX enhancements
NEWS 22	Feb 24	PCTGEN now available on STN
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NEWS 24	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS 25	Feb 26	PCTFULL now contains images
NEWS 26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 27	Mar 19	APOLLIT offering free connect time in April 2003
NEWS 28	Mar 20	EVENTLINE will be removed from STN
NEWS 29	Mar 24	PATDPAFULL now available on STN
NEWS 30	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
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FILE 'LIFESCI' ENTERED AT 11:23:02 ON 02 MAY 2003
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=> s "LDL receptor?"
L1        21973 "LDL RECEPTOR?"

=> s low (a) density
L2       224249 LOW (A) DENSITY

=> s l2 (a) lipoprotein
L3       156053 L2 (A) LIPOPROTEIN
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```
=> s l3 (a)receptor?
L4        17154 L3 (A) RECEPTOR?

=> s l1 or l4
L5        30924 L1 OR L4

=> s "p42/44MAPK"
L6          154 "P42/44MAPK"

=> s p42(w)44MAPK
L7          154 P42(W) 44MAPK

=> s l6 ot l7
MISSING OPERATOR L6 OT
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l6 or l7
L8          154 L6 OR L7

=> s l8 and l5
L9           21 L8 AND L5

=> dup rem l9
PROCESSING COMPLETED FOR L9
L10          11 DUP REM L9 (10 DUPLICATES REMOVED)

=> d 1-11 ibib ab

L10  ANSWER 1 OF 11     MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:   2003103037     IN-PROCESS
DOCUMENT NUMBER:    22503084   PubMed ID: 12562867
TITLE:              pp90RSK- and protein kinase C-dependent pathway regulates
                    p42/44MAPK-induced LDL
                    receptor transcription in HepG2 cells.
AUTHOR:             Kapoor Gurpreet S; Golden Carmen; Atkins Brett; Mehta Kamal
                    D
CORPORATE SOURCE:   Department of Molecular and Cellular Biochemistry, The Ohio
                    State University College of Medicine and Public Health, 464
                    Hamilton Hall, 1645 Neil Ave., Columbus, OH 43210.
SOURCE:             JOURNAL OF LIPID RESEARCH, (2003 Mar) 44 (3) 584-93.
                    Journal code: 0376606. ISSN: 0022-2275.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE:         Entered STN: 20030305
                    Last Updated on STN: 20030305
AB   We have previously shown that different extracellular stimuli require
     signaling through the Raf/MEK/p42/44MAPK cascade to
     induce LDL receptor expression.  The present studies
     were designed to delineate the molecular mechanisms underlying p42
     /44MAPK-induced LDL receptor transcription
     in HepG2-DeltaRaf-1:ER cells, a modified HepG2 cell line in which the
     Raf-1/MEK/p42/44MAPK cascade can be specifically
     activated by anti-estradiol ICI182,780 in an agonist-specific manner.
     Using these cells, we show that: a) LDL receptor
     induction was reduced in reporter constructs containing mutation in either
     Sp1 or sterol-regulatory element-1 (SRE-1) sites, whereas inactivation of
     both sites abolished the induction; b) E1A, which inhibits CREB binding
     protein (CBP), a common activator of SRE-1 binding protein and Sp1,
     strongly repressed the induction; c) intracellular inhibition of the 90
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kDa ribosomal S6 kinase (pp90RSK) cascade reduced **LDL receptor** induction; d) highly selective protein kinase C (PKC) inhibitors effectively abrogated the induction without affecting activation of pp90RSK; and e) overexpression of PKCbeta significantly induced **LDL receptor** promoter activity. Taken together, these results demonstrate that pp90RSK and PKCbeta are downstream effectors and Sp1, SRE-1 binding protein, and CBP are part of the transcriptional complex resulting in induction of **LDL receptor** expression in response to activation of the Raf/MEK/**p42/44MAPK** cascade. These findings identify for the first time a role for PKCbeta in determining the specificity of **p42/44MAPK** signaling by participating with pp90RSK in regulating gene expression.

L10 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:172156 HCAPLUS
DOCUMENT NUMBER: 136:195363
TITLE: Induction of **LDL receptor** expression in the HepG2-derived cell line by activation of extracellular-signal regulated kinase ERK-1/2
INVENTOR(S): Mehta, Kamal D.
PATENT ASSIGNEE(S): The Board of Trustees of the University of Arkansas, USA
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002018654	A1	20020307	WO 2001-US26982	20010829
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001085349	A5	20020313	AU 2001-85349	20010829
US 2002082192	A1	20020627	US 2001-942320	20010829
PRIORITY APPLN. INFO.:			US 2000-229271P P	20000830
			WO 2001-US26982 W	20010829

AB The present invention discloses that activation of extracellular-signal regulated kinase in the Raf-1/MEK/**p42/44MAPK** kinase cascade by ICI182780 induces low d. of lipoprotein (**LDL**) **receptor** expression, independent of other "upstream" factors or cell growth regulation, in the HepG2-derived cell line. The degree of **p42/44MAPK** activation dets. the extent of **LDL receptor** induction. The invention also provides a methods of inducing **LDL receptor** expression through the sole activation of extracellular-signal regulated kinase. The present findings underscore the important and central role of the MAPK pathway in regulating low d. lipoprotein receptor expression and may be of considerable potential significance for the development of new signal transduction-based approaches for the treatment of hypercholesterolemia.
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
ACCESSION NUMBER: 2002:318987 BIOSIS
DOCUMENT NUMBER: PREV200200318987
TITLE: Critical role of diacylglycerol- and phospholipid-regulated protein kinase Cepsilon in induction of **low-density lipoprotein receptor** transcription in response to depletion of cholesterol.
AUTHOR(S): Mehta, Kamal D. (1); Radominska-Pandya, Anna; Kapoor, Gurpreet S.; Dave, Bhuvanesh; Atkins, Brett A.
CORPORATE SOURCE: (1) Department of Molecular and Cellular Biochemistry, The Ohio State University College of Medicine, 1645 Neil Ave., 464 Hamilton Hall, Columbus, OH, 43210: mehta.80@osu.edu USA
SOURCE: Molecular and Cellular Biology, (June, 2002) Vol. 22, No. 11, pp. 3783-3793. http://mcb.asm.org/. print. ISSN: 0270-7306.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Induction of low-density lipoprotein (**LDL**) **receptor** transcription in response to depletion of cellular sterols in animal cells is well established. The intracellular signal or signals involved in regulating this process, however, remain unknown. Using a specific inhibitor of protein kinase C (PKC), calphostin C, we show the requirement of this kinase in the induction process in human hepatoma HepG2 cells. Overexpression of PKCepsilon, but not PKCalpha, -gamma, -delta, or -zeta was found to dramatically induce (approximately 18-fold) **LDL receptor** promoter activity. Interestingly, PKCepsilon-mediated induction was found to be sterol resistant. To further establish that PKCepsilon is involved in the sterol regulation of **LDL receptor** gene transcription, endogenous PKCepsilon was specifically inhibited by transfection with antisense PKCepsilon phosphorothionate oligonucleotides. Antisense treatment decreased endogenous PKCepsilon protein levels and completely blocked induction of **LDL receptor** transcription following sterol depletion. PKCepsilon-induced **LDL receptor** transcription is independent of the extracellular signal-regulated kinase 1 and 2 (**p42/44MAPK**) cascade, because the MEK-1/2 inhibitor, PD98059 did not inhibit, even though it blocked **p42/44MAPK** activation. Finally, photoaffinity labeling studies showed an isoform-specific interaction between PKCepsilon and sterols, suggesting that sterols may directly modulate its function by hampering binding of activators. This was confirmed by PKC activity assays. Altogether, these results define a novel signaling pathway leading to induction of **LDL receptor** transcription following sterol depletion, and a model is proposed to account for a new function for PKCepsilon as part of a sterol-sensitive signal transduction pathway in hepatic cells.

L10 ANSWER 4 OF 11 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2002419475 MEDLINE
DOCUMENT NUMBER: 22163340 PubMed ID: 12173743
TITLE: Role of mitogen-activated protein kinases and protein kinase C in regulating **low-density lipoprotein receptor** expression.
AUTHOR: Mehta Kamal D
CORPORATE SOURCE: Department of Molecular and Cellular Biochemistry, Ohio State University College of Medicine and Public Health, Columbus 43210, USA.. mehta.80@osu.edu
CONTRACT NUMBER: HL67760 (NHLBI)
SOURCE: GENE EXPRESSION, (2002) 10 (4) 153-64. Ref: 94
Journal code: 9200651. ISSN: 1052-2166.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20020814
Last Updated on STN: 20030313
Entered Medline: 20030312

AB The cell signaling pathways that culminate in induction of low-density lipoprotein (**LDL**) **receptor** transcription in response to a variety of extracellular and intracellular signals are beginning to be defined. Evidence is accumulating that **LDL receptor** transcription is under complex regulation and that a major pathway of induction by cytokines, growth factors, anisomycin, and phorbol esters involves the extracellular/mitogen-activated protein kinase (**p42/44MAPK**) cascade. In fact, degree of **p42/44MAPK** activation determines the extent of **LDL receptor** induction. The suppression of **LDL receptor** expression by stress-activated p38MAPK via **p42/44MAPK** provides a potential mechanism for stress-induced hypercholesterolemia observed in humans and animals. Moreover, endogenous signals such as cholesterol regulate **LDL receptor** transcription through a different signaling cascade involving protein kinase Cepsilon isoform (PKCepsilon). The ability of cholesterol to directly bind PKCepsilon in an isoform-specific manner strongly supports its role in sensing the cellular cholesterol levels. The emerging picture from the above studies is that regulation of **LDL receptor** transcription results from the activity of a number of interlinked regulatory molecules and pathways, rather than from a single linear series of events. These studies will provide the necessary framework for understanding differential responses within human populations to atherosclerosis following high-fat/cholesterol diet. This information may also provide new strategies to modulate specific gene expression with the hope to develop novel therapies for the treatment of hypercholesterolemia.

L10 ANSWER 5 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2003:186246 BIOSIS
DOCUMENT NUMBER: PREV200300186246
TITLE: Requirement of pp90RSK and protein kinase C in **p42/44MAPK**-induced **LDL receptor** transcription.
AUTHOR(S): Mehta, K. D. (1); Atkins, B. (1); Kapoor, G. S. (1)
CORPORATE SOURCE: (1) Molecular and Cellular Biochemistry, College of Medicine, Ohio State University, Columbus, OH, USA USA
SOURCE: Molecular Biology of the Cell, (Nov. 2002, 2002) Vol. 13, No. Supplement, pp. 17a. print.
Meeting Info.: 42nd Annual Meeting of the American Society for Cell Biology San Francisco, CA, USA December 14-18, 2002 American Society for Cell Biology
. ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L10 ANSWER 6 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4
ACCESSION NUMBER: 2002:483715 BIOSIS
DOCUMENT NUMBER: PREV200200483715
TITLE: Activation of Raf-1/MEK-1/2/**p42/44MAPK** cascade alone is sufficient to uncouple **LDL**

receptor expression from cell growth.
AUTHOR(S): Kapoor, Gurpreet S.; Atkins, Brett A.; Mehta, Kamal D. (1)
CORPORATE SOURCE: (1) Department of Molecular and Cellular Biochemistry, College of Medicine, Ohio State University, 1645 Neil Avenue, 464 Hamilton Hall, Columbus, OH, 43210: mehta.80@osu.edu USA
SOURCE: Molecular and Cellular Biochemistry, (July, 2002) Vol. 236, No. 1-2, pp. 13-22. http://www.kluweronline.com/issn/0300-8177. print.
ISSN: 0300-8177.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Our previous observation that induction of low density lipoprotein (**LDL**) **receptor** expression by a variety of extracellular signals is blocked by PD98059, a specific mitogen-activated protein kinase kinase inhibitor, led to the suggestion that the growth-responsive **p42/44MAPK** cascade plays a critical role in regulating **LDL receptor** transcription. To analyze the specific contribution of the **p42/44MAPK** cascade in regulating cell growth and **LDL receptor** induction, we established a HepG2-derived cell line that stably expresses an inducible form of oncogenic human Raf-1 kinase. Using this system, we provide direct evidence that specific activation of this cascade alone is not only required but is sufficient to fully induce **LDL receptor** expression. Interestingly, degree of **p42/44MAPK** activation determines the extent of **LDL receptor** induction. However, activation of **p42/44MAPK** in the above cells led to the inhibition of DNA synthesis, caused growth arrest, decrease in cyclin A and upregulation of p21Cip expression in a time-dependent manner. These results suggest that each of these two processes can be regulated independently of each other in response to **p42/44MAPK** activation. Thus, extent of **p42/44MAPK** activation may be important in transducing divergent cellular responses in human cells with implications for altered signaling resulting in hypercholesterolemia.

L10 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:725627 HCAPLUS
DOCUMENT NUMBER: 133:276357
TITLE: P38MAPK inhibitor and uses thereof
INVENTOR(S): Mehta, Kamal D.; Singh, Rajesh P.
PATENT ASSIGNEE(S): The Board of Trustees of the University of Arkansas, USA
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000059900	A1	20001012	WO 2000-US8775	20000331

W: AU, CA, JP, MX
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRIORITY APPLN. INFO.: US 1999-127343P P 19990401
AB The present invention demonstrates that p38MAPK inhibitor induces low d. lipoprotein receptor expression 6-8 fold, and further provides the application of such inhibitor in the treatment of hypercholesterolemia. The role of p38MAPK in the regulation of the **LDL receptor** expression was examd. to show that there is cross-talk

between **p42/44MAPK** and p38MAPK signalling cascades. P38MAPK neg. regulates **LDL receptor** expression via the **p42/44MAPK** signalling cascade.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5

ACCESSION NUMBER: 1999:385964 BIOSIS
DOCUMENT NUMBER: PREV199900385964
TITLE: One-way cross-talk between p38MAPK and **p42/44MAPK**. Inhibition of p38MAPK induces **low density lipoprotein receptor** expression through activation of the **p42/44MAPK** cascade.
AUTHOR(S): Singh, Rajesh P.; Dhawan, Punita; Golden, Carmen; Kapoor, Gurpreet S.; Mehta, Kamal D. (1)
CORPORATE SOURCE: (1) Dept. of Biochemistry and Molecular Biology, College of Medicine, Slot 516, University of Arkansas for Medical Sciences, 4301 W. Markham, Little Rock, AR, 72205 USA
SOURCE: Journal of Biological Chemistry, (July 9, 1999) Vol. 274, No. 28, pp. 19593-19600.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In this paper, we report that SB202190 alone, a specific inhibitor of p38MAPK, induces low density lipoprotein (**LDL**) **receptor** expression (6-8-fold) in a sterol-sensitive manner in HepG2 cells. Consistent with this finding, selective activation of the p38MAPK signaling pathway by expression of MKK6b(E), a constitutive activator of p38MAPK, significantly reduced **LDL receptor** promoter activity. Expression of the p38MAPK alpha-isoform had a similar effect, whereas expression of the p38MAPK betaII-isoform had no significant effect on **LDL receptor** promoter activity. SB202190-dependent increase in **LDL receptor** expression was accompanied by induction of **p42/44MAPK**, and inhibition of this pathway completely prevented SB202190-induced **LDL receptor** expression, suggesting that p38MAPK negatively regulates the **p42/44MAPK** cascade and the responses mediated by this kinase. Cross-talk between these kinases appears to be one-way because modulation of **p42/44MAPK** activity did not affect p38MAPK activation by a variety of stress inducers. Taken together, these findings reveal a hitherto unrecognized one-way communication that exists between p38MAPK and **p42/44MAPK** and provide the first evidence that through the **p42/44MAPK** signaling cascade, the p38MAPK alpha-isoform negatively regulates **LDL receptor** expression, thus representing a novel mechanism of fine tuning cellular levels of cholesterol in response to a diverse set of environmental cues.

L10 ANSWER 9 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 6

ACCESSION NUMBER: 2000:397321 BIOSIS
DOCUMENT NUMBER: PREV200000397321
TITLE: Critical role of **p42/44MAPK** activation in anisomycin and hepatocyte growth factor-induced **LDL receptor** expression: Activation of Raf-1/MEK-1/**p42/44MAPK** cascade alone is sufficient to induce **LDL receptor** expression.
AUTHOR(S): Dhawan, Punita; Bell, April; Kumar, Amit; Golden, Carmen;

Mehta, Kamal D. (1)
CORPORATE SOURCE: (1) Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, 4301 West Markham, Little Rock, AR, 72205 USA
SOURCE: Journal of Lipid Research, (Oct., 1999) Vol. 40, No. 10, pp. 1911-1919. print.
ISSN: 0022-2275.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The protein synthesis inhibitor anisomycin activates stress-related mitogen-activated protein kinases (MAPKs), namely, c-jun NH2-terminal kinase (p46/54JNK) and p38MAPK in mammalian cells. In this paper, we show that although exposure to anisomycin resulted in rapid and strong activation of p46/54JNK and p38MAPK, with a delayed low level dual-phosphorylation of mitogen/extracellular protein kinase (**p42/44MAPK**), low density lipoprotein (**LDL**) **receptor** induction depends solely on the mild activation of **p42/44MAPK** signaling cascade in HepG2 cells. Unlike hepatocyte growth factor (HGF) which caused **LDL receptor** induction via rapid, strong, and Ras-dependent **p42/44MAPK** activation, anisomycin-induced **p42/44MAPK** activity and increased **LDL receptor** expression in a Ras-independent manner. Finally, we examined the role of the **p42/44MAPK** signaling cascade in **LDL receptor** induction by activating this kinase independently of anisomycin or HGF. By using estrogen-dependent human Raf-1 protein kinase in transient transfection assays, we show that the exclusive activation of the Raf-1/MEK-1/**p42/44MAPK** signaling cascade with antiestrogen ICI 182,780 caused induction of **LDL receptor** expression to the same level as observed with either HGF or anisomycin. Consistent with the role of **p42/44MAPK**, induction was strongly inhibited by pretreatment with the MEK-1/2 inhibitor PD98059. Our observation that anisomycin can use **P42/44MAPK** signaling cascade is a departure from established thinking, and the results presented shows that activation of the **p42/44MAPK** alone is sufficient to fully induce **LDL receptor** transcription.

L10 ANSWER 10 OF 11 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 2000385963 MEDLINE
DOCUMENT NUMBER: 20338661 PubMed ID: 10881752
TITLE: Inhibition of stress-activated p38 mitogen-activated protein kinase induces **low-density lipoprotein receptor** expression.
AUTHOR: Mehta K D; Miller L
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock 72205, USA.
SOURCE: TRENDS IN CARDIOVASCULAR MEDICINE, (1999 Oct) 9 (7) 201-5.
Ref: 38
Journal code: 9108337. ISSN: 1050-1738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000818
Last Updated on STN: 20000818
Entered Medline: 20000809

AB We have recently shown that different signal transduction pathways initiated by a variety of agents converge on growth-responsive **p42/44MAPK** signaling cascade to induce low-density lipoprotein (**LDL**) **receptor** expression. Our recent demonstration that stress-activated p38MAPK negatively regulates **LDL receptor** expression in an isoform-specific manner via modulation of **p42/44MAPK** cascade represents a new dimension of complexity in the molecular communication that governs **LDL receptor** expression. The suggested one-way communication between p38MAPK and **p42/44MAPK** provides a potential mechanism for fine-tuning cellular levels of cholesterol in response to a diverse set of environmental cues, including stress. Cross talk between MAPKs opens new avenues toward understanding a variety of pathogenic processes; this makes them tempting targets for therapeutic interventions in cardiovascular diseases.

L10 ANSWER 11 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:167257 BIOSIS
DOCUMENT NUMBER: PREV199900167257
TITLE: **LDL receptor** expression is regulated positively by **P42/44MAPK** pathway in hepatic cells.
AUTHOR(S): Dhawan, P. (1); McMahon, M.; Mehta, K. D. (1)
CORPORATE SOURCE: (1) Dep. Biochemistry Molecular Biology, Univ. Ark. Med. Sciencdes 4301, West Markham St., Littlerock, AR 72205 USA
SOURCE: FASEB Journal, (March 12, 1999) Vol. 13, No. 4 PART 1, pp. A194.
Meeting Info.: Annual Meeting of the Professional Research Scientists for Experimental Biology 99 Washington, D.C., USA April 17-21, 1999
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English

=> d his

(FILE 'HOME' ENTERED AT 11:22:37 ON 02 MAY 2003)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 11:23:02 ON 02 MAY 2003

```
L1        21973 S "LDL RECEPTOR?"
L2       224249 S LOW (A) DENSITY
L3       156053 S L2 (A) LIPOPROTEIN
L4        17154 S L3 (A)RECEPTOR?
L5        30924 S L1 OR L4
L6          154 S "P42/44MAPK"
L7          154 S P42(W)44MAPK
L8          154 S L6 OR L7
L9           21 S L8 AND L5
L10          11 DUP REM L9 (10 DUPLICATES REMOVED)
```

=> e mehta k d/au

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E1           17     MEHTA K B/AU
E2          104     MEHTA K C/AU
E3          122 --> MEHTA K D/AU
E4           16     MEHTA K G/AU
E5            6     MEHTA K H/AU
E6            6     MEHTA K I/AU
E7           28     MEHTA K J/AU
E8           58     MEHTA K K/AU
E9           51     MEHTA K M/AU
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E10          61     MEHTA K N/AU
E11          95     MEHTA K P/AU
E12          22     MEHTA K R/AU

=> s e3
L11         122 "MEHTA K D"/AU

=> s l5 and l11
L12          58 L5 AND L11

=> s l7 and l12
L13           4 L7 AND L12

=> dup rem l13
PROCESSING COMPLETED FOR L13
L14           4 DUP REM L13 (0 DUPLICATES REMOVED)

=> d 1-4 ibib ab

L14  ANSWER 1 OF 4  BIOSIS  COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER:   2003:186246  BIOSIS
DOCUMENT NUMBER:    PREV200300186246
TITLE:              Requirement of pp90RSK and protein kinase C in p42
                    /44MAPK-induced LDL receptor
                    transcription.
AUTHOR(S):          Mehta, K. D. (1); Atkins, B. (1); Kapoor, G. S.
                    (1)
CORPORATE SOURCE:   (1) Molecular and Cellular Biochemistry, College of
                    Medicine, Ohio State University, Columbus, OH, USA USA
SOURCE:             Molecular Biology of the Cell, (Nov. 2002, 2002) Vol. 13,
                    No. Supplement, pp. 17a. print.
                    Meeting Info.: 42nd Annual Meeting of the American Society
                    for Cell Biology San Francisco, CA, USA December 14-18,
                    2002 American Society for Cell Biology
                    . ISSN: 1059-1524.
DOCUMENT TYPE:      Conference
LANGUAGE:           English

L14  ANSWER 2 OF 4  SCISEARCH  COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER:    1999:777984  SCISEARCH
THE GENUINE ARTICLE: 244BL
TITLE:               Critical role of p42/44(MAPK) activation in anisomycin and
                     hepatocyte growth factor-induced LDL
                     receptor expression: activation of
                     Raf-1/MEK-1/p42/44(MAPK) cascade alone is sufficient to
                     induce LDL receptor expression
AUTHOR:              Dhawan P; Bell A; Kumar A; Golden C; Mehta K D
                     (Reprint)
CORPORATE SOURCE:    UNIV ARKANSAS MED SCI, COLL MED, DEPT BIOCHEM & MOL BIOL,
                     4301 W MARKHAM, LITTLE ROCK, AR 72205 (Reprint); UNIV
                     ARKANSAS MED SCI, COLL MED, DEPT BIOCHEM & MOL BIOL,
                     LITTLE ROCK, AR 72205
COUNTRY OF AUTHOR:   USA
SOURCE:              JOURNAL OF LIPID RESEARCH, (OCT 1999) Vol. 40, No. 10, pp.
                     1911-1919.
                     Publisher: LIPID RESEARCH INC, 9650 ROCKVILLE PIKE,
                     BETHESDA, MD 20814-3998.
                     ISSN: 0022-2275.
DOCUMENT TYPE:       Article; Journal
FILE SEGMENT:        LIFE
LANGUAGE:            English
REFERENCE COUNT:     37
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ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The protein synthesis inhibitor anisomycin activates stress-related mitogen-activated protein kinases (MAPKs), namely, c-jun NH2-terminal kinase (p46/54(JNK)) and p38(MAPK) in mammalian cells, In this paper, we show that although exposure to anisomycin resulted in rapid and strong activation of p46/54(JNK) and p38(MAPK), with a delayed low level dual-phosphorylation of mitogen/extracellular protein kinase (p42/44(MAPK)), low density lipoprotein (**LDL**) **receptor** induction depends solely on the mild activation of **p42/44MAPK** Signaling cascade in HepC2 cells, Unlike hepatocyte growth factor (HGF) which caused **LDL receptor** induction via rapid, strong, and Ras-dependent **p42/44MAPK** activation, anisomycin-induced **p42/44MAPK** activity and increased **LDL receptor** expression in a Ras-independent manner. Finally, we examined the role of the **p42/44MAPK** signaling cascade in **LDL receptor** induction by activating this kinase independently of anisomycin or HGF, By using estrogen-dependent human Raf-1 protein kinase in transient transfection assays, we show that the exclusive activation of the Raf-1/MEK-1 /p42/44(MAPK) signaling cascade with antiestrogen ICI 182,780 caused induction of **LDL receptor** expression to the same level as observed with either HGF or anisomycin, Consistent with the role of p42/44(MAPK), induction was strongly inhibited by pretreatment with the MEK-1/2 inhibitor PD98059.jlr Our observation that anisomycin can use **p42/44MAPK** signaling cascade is a departure from established drinking, and the results presented shows that activation of the **p42/44MAPK** alone is sufficient to fully induce **LDL receptor** transcription., P., A. Bell, A. Kumar, C. Golden, and K. D. Mehta. Critical role of **p42/44MAPK** activation in anisomycin and hepatocyte growth factor-induced **LDL receptor** expression: activation of Raf-1/MEK-1/**p42/44MAPK** cascade alone is sufficient to induce **LDL receptor** expression.

L14 ANSWER 3 OF 4 MEDLINE

ACCESSION NUMBER: 2000385963 MEDLINE

DOCUMENT NUMBER: 20338661 PubMed ID: 10881752

TITLE: Inhibition of stress-activated p38 mitogen-activated protein kinase induces **low-density lipoprotein receptor** expression.

AUTHOR: **Mehta K D**; Miller L

CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock 72205, USA.

SOURCE: TRENDS IN CARDIOVASCULAR MEDICINE, (1999 Oct) 9 (7) 201-5. Ref: 38
Journal code: 9108337. ISSN: 1050-1738.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200008

ENTRY DATE: Entered STN: 20000818
Last Updated on STN: 20000818
Entered Medline: 20000809

AB We have recently shown that different signal transduction pathways initiated by a variety of agents converge on growth-responsive **p42/44MAPK** signaling cascade to induce low-density lipoprotein (**LDL**) **receptor** expression. Our recent demonstration that stress-activated p38MAPK negatively regulates **LDL**

receptor expression in an isoform-specific manner via modulation of **p42/44MAPK** cascade represents a new dimension of complexity in the molecular communication that governs **LDL receptor** expression. The suggested one-way communication between p38MAPK and **p42/44MAPK** provides a potential mechanism for fine-tuning cellular levels of cholesterol in response to a diverse set of environmental cues, including stress. Cross talk between MAPKs opens new avenues toward understanding a variety of pathogenic processes; this makes them tempting targets for therapeutic interventions in cardiovascular diseases.

L14 ANSWER 4 OF 4 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:167257 BIOSIS
DOCUMENT NUMBER: PREV199900167257
TITLE: **LDL receptor** expression is regulated positively by **P42/44MAPK** pathway in hepatic cells.
AUTHOR(S): Dhawan, P. (1); McMahon, M.; **Mehta, K. D. (1)**
CORPORATE SOURCE: (1) Dep. Biochemistry Molecular Biology, Univ. Ark. Med. Sciencdes 4301, West Markham St., Littlerock, AR 72205 USA
SOURCE: FASEB Journal, (March 12, 1999) Vol. 13, No. 4 PART 1, pp. A194.
Meeting Info.: Annual Meeting of the Professional Research Scientists for Experimental Biology 99 Washington, D.C., USA April 17-21, 1999
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English

=> d his

(FILE 'HOME' ENTERED AT 11:22:37 ON 02 MAY 2003)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 11:23:02 ON 02 MAY 2003

```
L1        21973 S "LDL RECEPTOR?"
L2       224249 S LOW (A) DENSITY
L3       156053 S L2 (A) LIPOPROTEIN
L4        17154 S L3 (A)RECEPTOR?
L5        30924 S L1 OR L4
L6          154 S "P42/44MAPK"
L7          154 S P42(W)44MAPK
L8          154 S L6 OR L7
L9           21 S L8 AND L5
L10          11 DUP REM L9 (10 DUPLICATES REMOVED)
                E MEHTA K D/AU
L11         122 S E3
L12          58 S L5 AND L11
L13           4 S L7 AND L12
L14           4 DUP REM L13 (0 DUPLICATES REMOVED)
```

=> s l8 and l11
L15 4 L8 AND L11

=> d 1-4 ibib ab

L15 ANSWER 1 OF 4 MEDLINE
ACCESSION NUMBER: 2000385963 MEDLINE
DOCUMENT NUMBER: 20338661 PubMed ID: 10881752
TITLE: Inhibition of stress-activated p38 mitogen-activated protein kinase induces low-density lipoprotein receptor

expression.
AUTHOR: **Mehta K D**; Miller L
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock 72205, USA.
SOURCE: TRENDS IN CARDIOVASCULAR MEDICINE, (1999 Oct) 9 (7) 201-5. Ref: 38
Journal code: 9108337. ISSN: 1050-1738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000818
Last Updated on STN: 20000818
Entered Medline: 20000809

AB We have recently shown that different signal transduction pathways initiated by a variety of agents converge on growth-responsive **p42/44MAPK** signaling cascade to induce low-density lipoprotein (LDL) receptor expression. Our recent demonstration that stress-activated p38MAPK negatively regulates LDL receptor expression in an isoform-specific manner via modulation of **p42/44MAPK** cascade represents a new dimension of complexity in the molecular communication that governs LDL receptor expression. The suggested one-way communication between p38MAPK and **p42/44MAPK** provides a potential mechanism for fine-tuning cellular levels of cholesterol in response to a diverse set of environmental cues, including stress. Cross talk between MAPKs opens new avenues toward understanding a variety of pathogenic processes; this makes them tempting targets for therapeutic interventions in cardiovascular diseases.

L15 ANSWER 2 OF 4 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2003:186246 BIOSIS
DOCUMENT NUMBER: PREV200300186246
TITLE: Requirement of pp90RSK and protein kinase C in **p42/44MAPK**-induced LDL receptor transcription.
AUTHOR(S): **Mehta, K. D. (1)**; Atkins, B. (1); Kapoor, G. S. (1)
CORPORATE SOURCE: (1) Molecular and Cellular Biochemistry, College of Medicine, Ohio State University, Columbus, OH, USA USA
SOURCE: Molecular Biology of the Cell, (Nov. 2002, 2002) Vol. 13, No. Supplement, pp. 17a. print.
Meeting Info.: 42nd Annual Meeting of the American Society for Cell Biology San Francisco, CA, USA December 14-18, 2002 American Society for Cell Biology
. ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L15 ANSWER 3 OF 4 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:167257 BIOSIS
DOCUMENT NUMBER: PREV199900167257
TITLE: LDL receptor expression is regulated positively by **P42/44MAPK** pathway in hepatic cells.
AUTHOR(S): Dhawan, P. (1); McMahon, M.; **Mehta, K. D. (1)**
CORPORATE SOURCE: (1) Dep. Biochemistry Molecular Biology, Univ. Ark. Med. Sciencdes 4301, West Markham St., Littlerock, AR 72205 USA
SOURCE: FASEB Journal, (March 12, 1999) Vol. 13, No. 4 PART 1, pp. A194.
Meeting Info.: Annual Meeting of the Professional Research

Scientists for Experimental Biology 99 Washington, D.C., USA April 17-21, 1999
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English

L15 ANSWER 4 OF 4 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 1999:777984 SCISEARCH
THE GENUINE ARTICLE: 244BL
TITLE: Critical role of p42/44(MAPK) activation in anisomycin and hepatocyte growth factor-induced LDL receptor expression: activation of Raf-1/MEK-1/p42/44(MAPK) cascade alone is sufficient to induce LDL receptor expression
AUTHOR: Dhawan P; Bell A; Kumar A; Golden C; **Mehta K D (Reprint)**
CORPORATE SOURCE: UNIV ARKANSAS MED SCI, COLL MED, DEPT BIOCHEM & MOL BIOL, 4301 W MARKHAM, LITTLE ROCK, AR 72205 (Reprint); UNIV ARKANSAS MED SCI, COLL MED, DEPT BIOCHEM & MOL BIOL, LITTLE ROCK, AR 72205
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF LIPID RESEARCH, (OCT 1999) Vol. 40, No. 10, pp. 1911-1919.
Publisher: LIPID RESEARCH INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998.
ISSN: 0022-2275.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 37

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The protein synthesis inhibitor anisomycin activates stress-related mitogen-activated protein kinases (MAPKs), namely, c-jun NH2-terminal kinase (p46/54(JNK)) and p38(MAPK) in mammalian cells, In this paper, we show that although exposure to anisomycin resulted in rapid and strong activation of p46/54(JNK) and p38(MAPK), with a delayed low level dual-phosphorylation of mitogen/extracellular protein kinase (p42/44(MAPK)), low density lipoprotein (LDL) receptor induction depends solely on the mild activation of **p42/44MAPK** Signaling cascade in HepC2 cells, Unlike hepatocyte growth factor (HGF) which caused LDL receptor induction via rapid, strong, and Ras-dependent **p42/44MAPK** activation, anisomycin-induced **p42/44MAPK** activity and increased LDL receptor expression in a Ras-independent manner. Finally, we examined the role of the **p42/44MAPK** signaling cascade in LDL receptor induction by activating this kinase independently of anisomycin or HGF, By using estrogen-dependent human Raf-1 protein kinase in transient transfection assays, we show that the exclusive activation of the Raf-1/MEK-1 /p42/44(MAPK) signaling cascade with antiestrogen ICI 182,780 caused induction of LDL receptor expression to the same level as observed with either HGF or anisomycin, Consistent with the role of p42/44(MAPK), induction was strongly inhibited by pretreatment with the MEK-1/2 inhibitor PD98059.jlr Our observation that anisomycin can use **p42/44MAPK** signaling cascade is a departure from established drinking, and the results presented shows that activation of the **p42/44MAPK** alone is sufficient to fully induce LDL receptor transcription., P., A. Bell, A. Kumar, C. Golden, and K. D. Mehta. Critical role of **p42/44MAPK** activation in anisomycin and hepatocyte growth factor-induced LDL receptor expression: activation of Raf-1/MEK-1/**p42/ 44MAPK** cascade alone is sufficient to induce LDL receptor expression.

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FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 11:23:02 ON 02 MAY 2003

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L1         21973 S "LDL RECEPTOR?"
L2        224249 S LOW (A) DENSITY
L3        156053 S L2 (A) LIPOPROTEIN
L4         17154 S L3 (A)RECEPTOR?
L5         30924 S L1 OR L4
L6           154 S "P42/44MAPK"
L7           154 S P42(W)44MAPK
L8           154 S L6 OR L7
L9            21 S L8 AND L5
L10           11 DUP REM L9 (10 DUPLICATES REMOVED)
                 E MEHTA K D/AU
L11          122 S E3
L12           58 S L5 AND L11
L13            4 S L7 AND L12
L14            4 DUP REM L13 (0 DUPLICATES REMOVED)
L15            4 S L8 AND L11

=> dup rem l12
PROCESSING COMPLETED FOR L12
L16           21 DUP REM L12 (37 DUPLICATES REMOVED)

=> d 1-21 ibib ab

L16  ANSWER 1 OF 21  SCISEARCH  COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER:    2003:239423  SCISEARCH
THE GENUINE ARTICLE: 653XF
TITLE:               pp90(RSK)- and protein kinase C-dependent pathway
                     regulates p42/44(MAPK)-induced LDL
                     receptor transcription in HepG2 cells
AUTHOR:              Kapoor G S; Golden C; Atkins B; Mehta K D
                     (Reprint)
CORPORATE SOURCE:    Ohio State Univ, Coll Med & Publ Hlth, Dept Mol & Cellular
                     Biochem, 464 Hamilton Hall, 1645 Neil Ave, Columbus, OH
                     43210 USA (Reprint); Ohio State Univ, Coll Med & Publ
                     Hlth, Dept Mol & Cellular Biochem, Columbus, OH 43210 USA
COUNTRY OF AUTHOR:   USA
SOURCE:              JOURNAL OF LIPID RESEARCH, (MAR 2003) Vol. 44, No. 3, pp.
                     584-593.
                     Publisher: LIPID RESEARCH INC, 9650 ROCKVILLE PIKE,
                     BETHESDA, MD 20814-3998 USA.
                     ISSN: 0022-2275.
DOCUMENT TYPE:       Article; Journal
LANGUAGE:            English
REFERENCE COUNT:     46
                    *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
```

AB We have previously shown that different extracellular stimuli require signaling through the Raf/MEK/p42/44(MAPK) cascade to induce LDL receptor expression. The present studies were designed to delineate the molecular mechanisms underlying p42/44(MAPK)-induced LDL receptor transcription in HepG2-DeltaRaf-1:ER cells, a modified HepG2 cell line in which the Raf-1/MEK/p42/44(MAPK) cascade can be specifically activated by anti-estradiol ICI182,780 in an agonist-specific manner. Using these cells, we show that: a) LDL receptor induction was reduced in reporter constructs containing mutation in either Sp1 or sterol-regulatory element-1 (SRE-1) sites, whereas inactivation of both sites abolished the induction; b) E1A, which inhibits CREB binding protein (CBP), a common activator of SRE-1 binding

protein and Sp1, strongly repressed the induction; c) intracellular inhibition of the 90 kDa ribosomal S6 kinase (pp90(RSK)) cascade reduced **LDL receptor** induction; d) highly selective protein kinase C (PKC) inhibitors effectively abrogated the induction without affecting activation of pp90RSK; and e) overexpression of PKCbeta significantly induced **LDL receptor** promoter activity. Taken together, these results demonstrate that pp90(RSK) and PKCbeta are downstream effectors and Sp1, SRE-1 binding protein, and CBP are part of the transcriptional complex resulting in induction of **LDL receptor** expression in response to activation of the Raf/MEK/p42/44(MAPK) cascade. These findings identify for the first time a role for PKC(3 in determining the specificity of p42/44(MAPK) signaling by participating with pp90RSK in regulating gene expression.

L16 ANSWER 2 OF 21 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 2002179351 EMBASE
TITLE: Critical role of diacylglycerol- and phospholipid-regulated protein kinase C.epsilon. in Induction of **low-density lipoprotein receptor** transcription in response to depletion of cholesterol.
AUTHOR: **Mehta K.D.**; Radominska-Pandya A.; Kapoor G.S.; Dave B.; Atkins B.A.
CORPORATE SOURCE: K.D. Mehta, Department of Cellular Biochemistry, Ohio State Univ. College of Medicine, 464 Hamilton Hall, 1645 Neil Ave., Columbus, OH 43210, United States. mehta.80@osu.edu
SOURCE: Molecular and Cellular Biology, (2002) 22/11 (3783-3793). Refs: 58
ISSN: 0270-7306 CODEN: MCEBD4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Induction of low-density lipoprotein (**LDL**) **receptor** transcription in response to depletion of cellular sterols in animal cells is well established. The intracellular signal or signals involved in regulating this process, however, remain unknown. Using a specific inhibitor of protein kinase C (PKC), calphostin C, we show the requirement of this kinase in the induction process in human hepatoma HepG2 cells. Overexpression of PKC.epsilon., but not PKC.alpha., -.gamma., -.delta., or .zeta. was found to dramatically induce (approximately 18-fold) **LDL receptor** promoter activity. Interestingly, PKC.epsilon.-mediated induction was found to be sterol resistant. To further establish that PKC.epsilon. is involved in the sterol regulation of **LDL receptor** gene transcription, endogenous PKC.epsilon. was specifically inhibited by transfection with antisense PKC.epsilon. phosphorothionate oligonucleotides. Antisense treatment decreased endogenous PKC.epsilon. protein levels and completely blocked induction of **LDL receptor** transcription following sterol depletion. PKC.epsilon.-induced **LDL receptor** transcription is independent of the extracellular signal-regulated kinase 1 and 2 (p42/44(MAPK)) cascade, because the MEK-1/2 inhibitor, PD98059 did not inhibit, even though it blocked p42/44(MAPK) activation. Finally, photoaffinity labeling studies showed an isoform-specific interaction between PKC.epsilon. and sterols, suggesting that sterols may directly modulate its function by hampering binding of activators. This was confirmed by PKC activity assays. Altogether, these results define a novel signaling pathway leading to induction of **LDL receptor** transcription following sterol depletion, and a model is proposed to account for a new function for PKC.epsilon. as part of a sterol-sensitive signal transduction pathway in hepatic cells.

L16 ANSWER 3 OF 21 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 2
ACCESSION NUMBER: 2002274870 EMBASE
TITLE: Role of mitogen-activated protein kinases and protein kinase C in regulating **low-density lipoprotein receptor** expression.
AUTHOR: **Mehta K.D.**
CORPORATE SOURCE: K.D. Mehta, Department of Cellular Biochemistry, Ohio State Univ. College of Medicine, Columbus, OH 43210, United States. mehta.80@osu.edu
SOURCE: Gene Expression, (2002) 10/4 (153-164).
Refs: 95
ISSN: 1052-2166 CODEN: GEEXEJ
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The cell signaling pathways that culminate in induction of low-density lipoprotein (**LDL**) **receptor** transcription in response to a variety of extracellular and intracellular signals are beginning to be defined. Evidence is accumulating that **LDL receptor** transcription is under complex regulation and that a major pathway of induction by cytokines, growth factors, anisomycin, and phorbol esters involves the extracellular/mitogen-activated protein kinase (p42/44(MAPK)) cascade. In fact, degree p42/44(MAPK) activation determines the extent of **LDL receptor** induction. The suppression of **LDL receptor** expression by stress-activated p38(MAPK) via p42/44(MAPK) provides a potential mechanism for stress-induced hypercholesterolemia observed in humans and animals. Moreover, endogenous signals such as cholesterol regulate **LDL receptor** transcription through a different signaling cascade involving protein kinase C.epsilon. isoform (PKC.epsilon.). The ability of cholesterol to directly bind PKC.epsilon. in an isoform-specific manner strongly supports its role in sensing the cellular cholesterol levels. The emerging picture from the above studies is that regulation of **LDL receptor** transcription results from the activity of a number of interlinked regulatory molecules and pathways, rather than from a single linear series of events. These studies will provide the necessary framework for understanding differential responses within human populations to atherosclerosis following high-fat/cholesterol diet. This information may also provide new strategies to modulate specific gene expression with the hope to develop novel therapies for the treatment of hypercholesterolemia.

L16 ANSWER 4 OF 21 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2003:186246 BIOSIS
DOCUMENT NUMBER: PREV200300186246
TITLE: Requirement of pp90RSK and protein kinase C in p42/44MAPK-induced **LDL receptor** transcription.
AUTHOR(S): **Mehta, K. D. (1)**; Atkins, B. (1); Kapoor, G. S. (1)
CORPORATE SOURCE: (1) Molecular and Cellular Biochemistry, College of Medicine, Ohio State University, Columbus, OH, USA USA
SOURCE: Molecular Biology of the Cell, (Nov. 2002, 2002) Vol. 13, No. Supplement, pp. 17a. print.
Meeting Info.: 42nd Annual Meeting of the American Society for Cell Biology San Francisco, CA, USA December 14-18, 2002 American Society for Cell Biology
. ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L16 ANSWER 5 OF 21 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 3
ACCESSION NUMBER: 2002279144 EMBASE
TITLE: Activation of Raf-1/MEK-1/2/p42/44(MAPK) cascade alone is sufficient to uncouple **LDL receptor** expression from cell growth.
AUTHOR: Kapoor G.S.; Atkins B.A.; **Mehta K.D.**
CORPORATE SOURCE: K.D. Mehta, Dept. of Molecular/Cell. Biochemist., Ohio State Univ. College Medicine, 464 Hamilton Hall, 1645 Neil Avenue, Columbus, OH 43210, United States. mehta.80@osu.edu
SOURCE: Molecular and Cellular Biochemistry, (2002) 236/1-2 (13-22).
Refs: 36
ISSN: 0300-8177 CODEN: MCBIB8
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Our previous observation that induction of low density lipoprotein (**LDL**) **receptor** expression by a variety of extracellular signals is blocked by PD98059, a specific mitogen-activated protein kinase kinase inhibitor, led to the suggestion that the growth-responsive p42/44(MAPK) cascade plays a critical role in regulating **LDL receptor** transcription. To analyze the specific contribution of the p42/44(MAPK) cascade in regulating cell growth and **LDL receptor** induction, we established a HepG2-derived cell line that stably expresses an inducible form of oncogenic human Raf-1 kinase. Using this system, we provide direct evidence that specific activation of this cascade alone is not only required but is sufficient to fully induce **LDL receptor** expression. Interestingly, degree of p42/44(MAPK) activation determines the extent of **LDL receptor** induction. However, activation of p42/44(MAPK) in the above cells led to the inhibition of DNA synthesis, caused growth arrest, decrease in cyclin A and upregulation of p21(Cip) expression in a time-dependent manner. These results suggest that each of these two processes can be regulated independently of each other in response to p42/44(MAPK) activation. Thus, extent of p42/44(MAPK) activation may be important in transducing divergent cellular responses in human cells with implications for altered signaling resulting in hypercholesterolemia.

L16 ANSWER 6 OF 21 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000226341 EMBASE
TITLE: Inhibition of stress-activated p38 mitogen-activated protein kinase induces **low-density lipoprotein receptor** expression.
AUTHOR: **Mehta K.D.**; Miller L.
CORPORATE SOURCE: K.D. Mehta, Dept. Biochemistry/Molecular Biology, College of Medicine, University of Arkansas, 4301 West Markham, Little Rock, AR 72205, United States
SOURCE: Trends in Cardiovascular Medicine, (2000) 9/7 (201-205).
Refs: 38
ISSN: 1050-1738 CODEN: TCMDEQ
PUBLISHER IDENT.: S 1050-1738(00)00021-9
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
025 Hematology
029 Clinical Biochemistry
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We have recently shown that different signal transduction pathways initiated by a variety of agents converge on growth-responsive p42/44(MAPK) signaling cascade to induce low-density lipoprotein (**LDL**) **receptor** expression. Our recent demonstration that stress-activated p38(MAPK) negatively regulates **LDL receptor** expression in an isoform-specific manner via modulation of p42/44(MAPK) cascade represents a new dimension of complexity in the molecular communication that governs **LDL receptor** expression. The suggested one-way communication between p38(MAPK) and p42/44(MAPK) provides a potential mechanism for fine-tuning cellular levels of cholesterol in response to a diverse set of environmental cues, including stress. Cross talk between MAPKs opens new avenues toward understanding a variety of pathogenic processes; this makes them tempting targets for therapeutic interventions in cardiovascular diseases.

L16 ANSWER 7 OF 21 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4

ACCESSION NUMBER: 1999:173132 BIOSIS
DOCUMENT NUMBER: PREV199900173132
TITLE: Cis-acting element in the human **LDL receptor** promoter and uses thereof.
AUTHOR(S): **Mehta, K. D.**
CORPORATE SOURCE: Little Rock, Ark. USA
ASSIGNEE: THE UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES
PATENT INFORMATION: US 5879879 March 9, 1999
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (March 9, 1999) Vol. 1220, No. 2, pp. 1492. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English

L16 ANSWER 8 OF 21 MEDLINE DUPLICATE 5

ACCESSION NUMBER: 1999321880 MEDLINE
DOCUMENT NUMBER: 99321880 PubMed ID: 10391894
TITLE: One-way cross-talk between p38(MAPK) and p42/44(MAPK). Inhibition of p38(MAPK) induces **low density lipoprotein receptor** expression through activation of the p42/44(MAPK) cascade.
AUTHOR: Singh R P; Dhawan P; Golden C; Kapoor G S; **Mehta K D**
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, USA.
CONTRACT NUMBER: HL-51592 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Jul 9) 274 (28) 19593-600.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990816
Last Updated on STN: 20000303
Entered Medline: 19990805

AB In this paper, we report that SB202190 alone, a specific inhibitor of p38(MAPK), induces low density lipoprotein (**LDL**) **receptor** expression (6-8-fold) in a sterol-sensitive manner in HepG2 cells. Consistent with this finding, selective activation of the p38(MAPK) signaling pathway by expression of MKK6b(E), a constitutive activator of p38(MAPK), significantly reduced **LDL**

receptor promoter activity. Expression of the p38(MAPK) alpha-isoform had a similar effect, whereas expression of the p38(MAPK) betaII-isoform had no significant effect on **LDL receptor** promoter activity. SB202190-dependent increase in **LDL receptor** expression was accompanied by induction of p42/44(MAPK), and inhibition of this pathway completely prevented SB202190-induced **LDL receptor** expression, suggesting that p38(MAPK) negatively regulates the p42/44(MAPK) cascade and the responses mediated by this kinase. Cross-talk between these kinases appears to be one-way because modulation of p42/44(MAPK) activity did not affect p38(MAPK) activation by a variety of stress inducers. Taken together, these findings reveal a hitherto unrecognized one-way communication that exists between p38(MAPK) and p42/44(MAPK) and provide the first evidence that through the p42/44(MAPK) signaling cascade, the p38(MAPK) alpha-isoform negatively regulates **LDL receptor** expression, thus representing a novel mechanism of fine tuning cellular levels of cholesterol in response to a diverse set of environmental cues.

L16 ANSWER 9 OF 21 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 1999438160 MEDLINE
DOCUMENT NUMBER: 99438160 PubMed ID: 10508211
TITLE: Critical role of p42/44(MAPK) activation in anisomycin and hepatocyte growth factor-induced **LDL receptor** expression: activation of Raf-1/Mek-1/p42/44(MAPK) cascade alone is sufficient to induce **LDL receptor** expression.
AUTHOR: Dhawan P; Bell A; Kumar A; Golden C; **Mehta K D**
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, 4301 West Markham, Little Rock, AR 72205, USA.
CONTRACT NUMBER: HL-51592-04 (NHLBI)
SOURCE: JOURNAL OF LIPID RESEARCH, (1999 Oct) 40 (10) 1911-9. Journal code: 0376606. ISSN: 0022-2275.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20020420
Entered Medline: 19991223

AB The protein synthesis inhibitor anisomycin activates stress-related mitogen-activated protein kinases (MAPKs), namely, c-jun NH(2)-terminal kinase (p46/54(JNK)) and p38(MAPK) in mammalian cells. In this paper, we show that although exposure to anisomycin resulted in rapid and strong activation of p46/54(JNK) and p38(MAPK), with a delayed low level dual-phosphorylation of mitogen/extracellular protein kinase (p42/44(MAPK)), low density lipoprotein (**LDL**) **receptor** induction depends solely on the mild activation of p42/44(MAPK) signaling cascade in HepG2 cells. Unlike hepatocyte growth factor (HGF) which caused **LDL receptor** induction via rapid, strong, and Ras-dependent p42/44(MAPK) activation, anisomycin-induced p42/44(MAPK) activity and increased **LDL receptor** expression in a Ras-independent manner. Finally, we examined the role of the p42/44(MAPK) signaling cascade in **LDL receptor** induction by activating this kinase independently of anisomycin or HGF. By using estrogen-dependent human Raf-1 protein kinase in transient transfection assays, we show that the exclusive activation of the Raf-1/MEK-1/p42/44(MAPK) signaling cascade with antiestrogen ICI 182, 780 caused induction of **LDL receptor** expression to the same level as observed with either HGF or anisomycin. Consistent with the role of p42/44(MAPK), induction was strongly inhibited by pretreatment with the

MEK-1/2 inhibitor PD98059.Our observation that anisomycin can use p42/44(MAPK) signaling cascade is a departure from established thinking, and the results presented shows that activation of the p42/44(MAPK) alone is sufficient to fully induce **LDL receptor** transcription.

L16 ANSWER 10 OF 21 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 2000385963 MEDLINE
DOCUMENT NUMBER: 20338661 PubMed ID: 10881752
TITLE: Inhibition of stress-activated p38 mitogen-activated protein kinase induces **low-density lipoprotein receptor** expression.
AUTHOR: **Mehta K D**; Miller L
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock 72205, USA.
SOURCE: TRENDS IN CARDIOVASCULAR MEDICINE, (1999 Oct) 9 (7) 201-5. Ref: 38
Journal code: 9108337. ISSN: 1050-1738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000818
Last Updated on STN: 20000818
Entered Medline: 20000809

AB We have recently shown that different signal transduction pathways initiated by a variety of agents converge on growth-responsive p42/44MAPK signaling cascade to induce low-density lipoprotein (**LDL**) **receptor** expression. Our recent demonstration that stress-activated p38MAPK negatively regulates **LDL receptor** expression in an isoform-specific manner via modulation of p42/44MAPK cascade represents a new dimension of complexity in the molecular communication that governs **LDL receptor** expression. The suggested one-way communication between p38MAPK and p42/44MAPK provides a potential mechanism for fine-tuning cellular levels of cholesterol in response to a diverse set of environmental cues, including stress. Cross talk between MAPKs opens new avenues toward understanding a variety of pathogenic processes; this makes them tempting targets for therapeutic interventions in cardiovascular diseases.

L16 ANSWER 11 OF 21 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:167257 BIOSIS
DOCUMENT NUMBER: PREV199900167257
TITLE: **LDL receptor** expression is regulated positively by P42/44MAPK pathway in hepatic cells.
AUTHOR(S): Dhawan, P. (1); McMahon, M.; **Mehta, K. D. (1)**
CORPORATE SOURCE: (1) Dep. Biochemistry Molecular Biology, Univ. Ark. Med. Sciencdes 4301, West Markham St., Littlerock, AR 72205 USA
SOURCE: FASEB Journal, (March 12, 1999) Vol. 13, No. 4 PART 1, pp. A194.
Meeting Info.: Annual Meeting of the Professional Research Scientists for Experimental Biology 99 Washington, D.C., USA April 17-21, 1999
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English

L16 ANSWER 12 OF 21 SCISEARCH COPYRIGHT 2003 THOMSON ISI

ACCESSION NUMBER: 1999:808341 SCISEARCH
THE GENUINE ARTICLE: 226QW
TITLE: **Ldl receptor** expression is regulated positively by p42/44(MAPK) pathway in hepatic cells.
AUTHOR: Dhawan P (Reprint); McMahon M; **Mehta K D**
CORPORATE SOURCE: UNIV ARKANSAS MED SCI, DEPT BIOCHEM & MOL BIOL, LITTLE ROCK, AR 72205; UNIV CALIF SAN FRANCISCO, CANC RES INST, SAN FRANCISCO, CA 94145
COUNTRY OF AUTHOR: USA
SOURCE: FASEB JOURNAL, (12 MAR 1999) Vol. 13, No. 4, Part 1, Supp. [S], pp. A194-A194.
Publisher: FEDERATION AMER SOC EXP BIOL, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998.
ISSN: 0892-6638.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 0

L16 ANSWER 13 OF 21 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 1998288318 MEDLINE
DOCUMENT NUMBER: 98288318 PubMed ID: 9624172
TITLE: Differential roles of extracellular signal-regulated kinase-1/2 and p38(MAPK) in interleukin-1beta- and tumor necrosis factor-alpha-induced **low density lipoprotein receptor** expression in HepG2 cells.
AUTHOR: Kumar A; Middleton A; Chambers T C; **Mehta K D**
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, USA.
CONTRACT NUMBER: HL-51592-04 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Jun 19) 273 (25) 15742-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980716
Last Updated on STN: 20000303
Entered Medline: 19980709

AB The inflammatory cytokines interleukin-1beta (IL-1beta) and tumor necrosis factor-alpha (TNF), elevated in inflammatory, malignant, and infectious diseases, induce low density lipoprotein (**LDL**) **receptor** transcription in HepG2 cells, and such an induction can account for hypocholesterolemia associated with these states. However, the signaling mechanisms of cytokine-mediated **LDL receptor** induction are largely unexplored. In the present studies, we examined the potential involvement of different mitogen-activated protein kinase (MAPK) pathways. Northern analysis demonstrated that IL-1beta or TNF significantly increased **LDL receptor** transcript in HepG2 cells, whereas expression of another tightly regulated sterol-responsive squalene synthase gene was unaffected. IL-1beta treatment resulted in transient activation of three MAPK cascades, namely p46/54(JNK), p38(MAPK), and ERK-1/2, with maximal activation of 20-, 25-, and 3-fold, respectively, occurring 15-30 min after cytokine addition. PD98059, a specific inhibitor of MAPK kinase activity, inhibited IL-1beta-induced **LDL receptor** expression. In contrast, SB202190, a specific inhibitor of p38(MAPK), enhanced IL-1beta-induced **LDL receptor** expression, with a concomitant increase in ERK-1/2 activity. Similarly,

TNF induced **LDL receptor** expression also required ERK-1/2 activation. Finally, sterols repressed IL-1beta induced receptor expression, without affecting ERK-1/2 activation. These results show that IL-1beta- or TNF-induced **LDL receptor** expression requires ERK-1/2 activation, that the p38(MAPK) pathway negatively regulates **LDL receptor** expression, and that sterols inhibit induction at a point downstream of ERK-1/2 in HepG2 cells.

L16 ANSWER 14 OF 21 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 97465961 MEDLINE
DOCUMENT NUMBER: 97465961 PubMed ID: 9321669
TITLE: Identification of essential nucleotides of the FP1 element responsible for enhancement of **low density lipoprotein receptor** gene transcription.
AUTHOR: Dhawan P; Chang R; **Mehta K D**
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, 4301 West Markham, Little Rock, AR 72205, USA.
CONTRACT NUMBER: HL51592-04 (NHLBI)
SOURCE: NUCLEIC ACIDS RESEARCH, (1997 Oct 15) 25 (20) 4132-8. Journal code: 0411011. ISSN: 0305-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971202

AB Low density lipoprotein (**LDL**) **receptor** gene is regulated at the transcriptional level by the intracellular level of sterols in animal cells. We have recently identified a 20 bp long region (-145 to -126), designated Footprint 1 (FP1), participating in maximal expression of the human **LDL receptor** gene in the absence of sterols in HepG2 cells [Mehta, K. D., Chang, R., Underwood, J., Wise, J. and Kumar, A. (1996) J. Biol. Chem ., 271, 33616-33622]. To determine the minimal FP1 sequence and to define the critical nucleotides required for function, a series of single nucleotide substitutions were introduced in the FP1 region. Twenty-three independent mutations were analyzed by transfection into HepG2 cells. These studies localize the regulatory region to 14 bp and demonstrate the requirement for essential guanine nucleotides at positions -135 and -136 for FP1 function. Furthermore, transfection studies suggest that the FP1-dependent increase in reporter gene expression is possibly mediated through interaction with the sterol-regulatory element. UV cross-linking and Southwestern blot analysis identified FP1-binding factors of approximately 50 and 125 kDa, which we have denoted p50 and p125. Mutations of the critical guanine residues (-135/-136) decreased the formation of the specific protein-DNA complex with the FP1 sequence and abolished its binding to the p125. We conclude that direct interaction of the p125 factor with these nucleotides of the FP1 element potentially contributes to FP1-dependent induction of **LDL receptor** gene expression.

L16 ANSWER 15 OF 21 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 1998052315 MEDLINE
DOCUMENT NUMBER: 98052315 PubMed ID: 9392422
TITLE: Phorbol ester-induced **low density lipoprotein receptor** gene expression in HepG2 cells involves protein kinase C-mediated p42/44 MAP kinase activation.

AUTHOR: Kumar A; Chambers T C; Cloud-Heflin B A; **Mehta K D**
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock 72205-7199, USA.
CONTRACT NUMBER: HL-51592-04 (NHLBI)
SOURCE: JOURNAL OF LIPID RESEARCH, (1997 Nov) 38 (11) 2240-8.
Journal code: 0376606. ISSN: 0022-2275.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980217
Last Updated on STN: 20000303
Entered Medline: 19980130

AB The signaling pathway involved in low density lipoprotein (**LDL**) **receptor** gene expression induced by the phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA) was investigated in the human hepatoma HepG2 cell line. Treatment of HepG2 cells with 100 nM TPA resulted in an approximately 20-fold increase in **LDL receptor** mRNA level, as determined by RT-PCR, which peaked at 2-4 h of treatment and subsequently declined. The protein kinase C (PKC) inhibitors calphostin C and staurosporine prevented TPA-mediated **LDL receptor** mRNA induction. In contrast, TPA did not affect squalene synthase mRNA expression. Immunoblotting of cell extracts with isozyme-specific PKC antibodies revealed that HepG2 cells expressed PKC alpha, which was mainly cytosolic, and PKC beta, PK epsilon, and PKC zeta, all of which were present in both the cytosolic and particulate fractions. Treatment of HepG2 cells with 100 nM TPA resulted in translocation of cytosolic PKC alpha to the particulate fraction, with a maximum at 30 min-2 h of treatment, but was without effect on the subcellular distribution of the other isozymes. TPA treatment also led to activation of the mitogen-activated protein kinase (MAPK) ERK cascade. The specific MAPK pathway inhibitor PD98059 blocked TPA-induced ERK activation. Furthermore, pretreatment of cells with PD98059 inhibited TPA-induced **LDL receptor** mRNA induction. Moreover, pretreatment of cells with calphostin C inhibited TPA-mediated ERK activation and **LDL receptor** mRNA induction in a dose-dependent fashion. Based on a close kinetic correlation between PKC alpha translocation and ERK activation, and the effects of specific inhibitors, these findings suggest that translocation/activation of PKC alpha, and subsequent activation of the Raf-1/MEK/ERK MAPK cascade, represent key events in the transcriptional induction of **LDL receptor** gene by TPA in HepG2 cells.

L16 ANSWER 16 OF 21 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 97126008 MEDLINE
DOCUMENT NUMBER: 97126008 PubMed ID: 8969230
TITLE: Identification of a novel cis-acting element participating in maximal induction of the human **low density lipoprotein receptor** gene transcription in response to low cellular cholesterol levels.
AUTHOR: **Mehta K D**; Chang R; Underwood J; Wise J; Kumar A
CORPORATE SOURCE: Department of Biochemistry, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Dec 27) 271 (52) 33616-22.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970128

AB In this paper, we present both in vivo and in vitro evidence for the presence of a novel cis-acting regulatory element that is required for maximal induction of the human low density lipoprotein (**LDL**) **receptor** gene following depletion of cellular sterols in HepG2 cells. First, in vivo dimethyl sulfate footprinting of the human **LDL receptor** promoter before and after transcriptional induction in HepG2 cells revealed protection from -145 to -126, 5'-GAGCTTCACGGGTTAAAAAG-3' (referred to as FP1 site). Second, transient transfections of HepG2 cells with promoter luciferase reporter constructs containing the FP1 site resulted in significant enhancement (approximately 375%) of reporter gene expression in response to low levels of sterols compared with parallel plasmid without the FP1 site. In addition, this response was markedly attenuated on nucleotide substitutions within the FP1 site. Third, by electrophoretic mobility shift assays, the FP1 sequence was found to bind protein(s) from HepG2 nuclear extracts in a sequence-specific manner. In vitro binding of the FP1 mutants paralleled the results obtained for their in vivo transcription. On the basis of competition profiles, the FP1-binding factor is different from the known transcription factors binding to the AT-rich CArG and GArC motifs. Furthermore, the FP1-binding protein is not specific to HepG2 cells because nuclear factor(s) with the same specificity was observed in nuclear extracts of non-hepatic HeLa cells. We conclude that transcriptional induction of the **LDL receptor** gene in response to sterol depletion is mediated, in part, by an highly conserved novel cis-acting element through the binding of specific nuclear protein(s).

L16 ANSWER 17 OF 21 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 96158953 MEDLINE
DOCUMENT NUMBER: 96158953 PubMed ID: 8579582
TITLE: In vivo role of the Sp1 site neighboring sterol-responsive element-1 in controlling **low-density lipoprotein receptor** gene expression.
AUTHOR: Chang R; Yang E; Chamblis D; Kumar A; Wise J; **Mehta K D**
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, College of Medicine, Little Rock 72205, USA.
CONTRACT NUMBER: HL51592 (NHLBI)
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1996 Jan 26) 218 (3) 733-9.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960321
Last Updated on STN: 19960321
Entered Medline: 19960312

AB The in vivo role of the crucial Sp1 site neighboring sterol-responsive element-1 (SRE-1) in controlling **LDL receptor** gene expression in the presence or absence of sterols was examined. For this purpose the Xenopus laevis system was utilized as there are two different genes for **LDL receptors** in frogs which differ in their promoter region in the Sp1-binding sequence of repeat 3 present

immediately adjacent to SRE-1. DNase I footprinting of promoters of both receptors showed differences in the affinity of this Sp1 site to purified transcription factor Sp1. Transcript levels of both **LDL receptors** were measured in livers of frogs on normal and cholesterol-enriched diets. Basal levels and extent of repression of **LDL receptor** gene on sterol administration were found to be dependent on the nature of the Sp1 site of repeat 3 under in vivo conditions. We conclude that this Sp1 site acts as a constitutive positive transcriptional element that forms a part of the active transcription complex irrespective of cellular sterol levels.

L16 ANSWER 18 OF 21 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 97077311 MEDLINE
DOCUMENT NUMBER: 97077311 PubMed ID: 8919878
TITLE: Chiloscyllium plagiosum **low-density lipoprotein receptor**: evolutionary conservation of five different functional domains.
AUTHOR: **Mehta K D**; Chang R; Norman J
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock 72205, USA.
SOURCE: JOURNAL OF MOLECULAR EVOLUTION, (1996 Feb) 42 (2) 264-72. Journal code: 0360051. ISSN: 0022-2844.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-L36118
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19980206
Entered Medline: 19961231

AB All five functional domains of the low-density lipoprotein (**LDL**) **receptor** were assembled in their modern form more than 450 million years ago, as revealed from the cloning and sequencing of an **LDL receptor** cDNA from Chiloscyllium plagiosum (banded cat shark). The shark **LDL receptor** has the same overall architecture as the mammalian and amphibian counterparts. Each of the seven cysteine-rich repeats in the ligand binding domain resembles its counterpart in the human **LDL receptor** more than it does the other repeats in the shark receptor as suggested by the presence of unique "signature" sequences, indicating that these repeats had already acquired their independent structures by the time of shark development. Furthermore, amino acid sequences of the entire ligand binding domain of shark **LDL receptor** show 35% identity over a stretch of 294 residues with a Lymnaea stagnalis G-protein-linked receptor (LSGLR). The region of homology between these unrelated proteins includes conservation of most of the unique characteristics of the cysteine-rich repeats of **LDL receptor** at the expected positions in LSGLR. The results presented are consistent with the hypothesis that all seven repeats in the ligand binding domain of **LDL receptor** may have been lifted directly from an ancestral gene instead of being evolutionary duplications of a single repeat recruited by the primitive **LDL receptor** from another gene.

L16 ANSWER 19 OF 21 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 95:769330 SCISEARCH
THE GENUINE ARTICLE: TB480
TITLE: IN-VIVO FOOTPRINTING OF HUMAN **LDL RECEPTOR** GENE PROMOTER - IMPLICATION FOR STEROL REGULATION OF GENE-EXPRESSION
AUTHOR: **MEHTA K D (Reprint)**; CHANG R X

CORPORATE SOURCE: UNIV ARKANSAS, COLL MED, LITTLE ROCK, AR, 72204
COUNTRY OF AUTHOR: USA
SOURCE: CIRCULATION, (15 OCT 1995) Vol. 92, No. 8, Supp. S, pp. 1724.
ISSN: 0009-7322.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L16 ANSWER 20 OF 21 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 91244816 MEDLINE
DOCUMENT NUMBER: 91244816 PubMed ID: 1709932
TITLE: The **low density lipoprotein receptor** in Xenopus laevis. II. Feedback repression mediated by conserved sterol regulatory element.
AUTHOR: **Mehta K D**; Brown M S; Bilheimer D W; Goldstein J L
CORPORATE SOURCE: Department of Molecular Genetics, University of Texas, Southwestern Medical Center, Dallas 75235.
CONTRACT NUMBER: HL 20948 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1991 Jun 5) 266 (16) 10415-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-M62977; GENBANK-M62979; GENBANK-M63255; GENBANK-M64332; GENBANK-S69601; GENBANK-S69604; GENBANK-S69828; GENBANK-S69830; GENBANK-S78749; GENBANK-S78751
ENTRY MONTH: 199107
ENTRY DATE: Entered STN: 19910719
Last Updated on STN: 19970203
Entered Medline: 19910701

AB The 5'-flanking regions of the two low density lipoprotein (**LDL**) **receptor** genes in Xenopus laevis contain three repeat sequences that are virtually identical to the repeats that mediate sterol-regulated transcription of the human **LDL receptor** gene. Like their human counterparts, Xenopus repeats 1 and 3, but not repeat 2, bind the transcription factor Sp1 and thus probably function as positive transcription elements. Xenopus repeat 2, like human repeat 2, contains all of the nucleotides that are required for sterol regulation. Administration of sterols repressed Xenopus **LDL receptor** mRNA in cultured A6 kidney cells and in the liver of intact frogs. In frogs this repression was associated with a 2-fold increase in plasma LDL levels. Xenopus LDL contains a protein corresponding in size to human apoB-100, a ligand for the **LDL receptor**. We found no evidence that frog plasma contains B-48, nor did we observe a clear-cut protein corresponding to apoE. We conclude that the structural gene for the **LDL receptor** has been under sterol-mediated regulation at least since the time of amphibian development more than 350 million years ago.

L16 ANSWER 21 OF 21 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 91244815 MEDLINE
DOCUMENT NUMBER: 91244815 PubMed ID: 1709931
TITLE: The **low density lipoprotein receptor** in Xenopus laevis. I. Five domains that resemble the human receptor.
AUTHOR: **Mehta K D**; Chen W J; Goldstein J L; Brown M S

CORPORATE SOURCE: Department of Molecular Genetics, University of Texas Southwestern Medical Center, Dallas 75235.
CONTRACT NUMBER: HL 20948 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1991 Jun 5) 266 (16) 10406-14.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-M62976; GENBANK-M62978; GENBANK-M63255; GENBANK-M64332; GENBANK-S69601; GENBANK-S69604; GENBANK-S69828; GENBANK-S69830; GENBANK-S78749; GENBANK-S78751
ENTRY MONTH: 199107
ENTRY DATE: Entered STN: 19910719
Last Updated on STN: 19960129
Entered Medline: 19910701

AB All five functional domains of the low density lipoprotein (**LDL**) **receptor** were assembled in their modern form more than 350 million years ago, as revealed from the sequence of two cloned cDNAs from the frog Xenopus laevis. The two cDNAs appear to represent duplicated copies of the **LDL receptor** gene that arose when the entire genome of Xenopus duplicated approximately 30 million years ago. Both frog **LDL receptors** bound Xenopus LDL with high affinity and human LDL with lower affinity when expressed in monkey COS cells. The receptors also showed high affinity for rabbit beta-migrating very low density lipoprotein and canine apoE-HDLc, both of which contain apolipoprotein E. Each of the seven cysteine-rich repeats in the ligand binding domain of the Xenopus receptors resembles its counterpart in the human, indicating that these repeats had already acquired their independent structures by the time of amphibian development. The cytoplasmic tail of both Xenopus receptors is 86% identical to the human, including the FDNPVY sequence necessary for internalization in coated pits. The attainment of a fully developed receptor structure in Xenopus suggests that earlier forms of the receptor may exist in animals that are older than amphibians. An accompanying paper demonstrates that expression of both Xenopus receptor genes is controlled by a sterol regulatory element that closely resembles the human sequence (Mehta, K.D., Brown, M.S., Bilheimer, D.W., and Goldstein, J.L. (1991) J. Biol. Chem. 266, 10415-10419).

=> d his

(FILE 'HOME' ENTERED AT 11:22:37 ON 02 MAY 2003)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 11:23:02 ON 02 MAY 2003

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L1        21973 S "LDL RECEPTOR?"
L2       224249 S LOW (A) DENSITY
L3       156053 S L2 (A) LIPOPROTEIN
L4        17154 S L3 (A)RECEPTOR?
L5        30924 S L1 OR L4
L6          154 S "P42/44MAPK"
L7          154 S P42(W)44MAPK
L8          154 S L6 OR L7
L9           21 S L8 AND L5
L10          11 DUP REM L9 (10 DUPLICATES REMOVED)
                E MEHTA K D/AU
L11         122 S E3
L12          58 S L5 AND L11
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L13            4 S L7 AND L12
L14            4 DUP REM L13 (0 DUPLICATES REMOVED)
L15            4 S L8 AND L11
L16           21 DUP REM L12 (37 DUPLICATES REMOVED)

=> s l16 and MAPK
L17           13 L16 AND MAPK

=> d 1-13 ibib ab

L17  ANSWER 1 OF 13     MEDLINE
ACCESSION NUMBER:    2000385963     MEDLINE
DOCUMENT NUMBER:     20338661   PubMed ID: 10881752
TITLE:               Inhibition of stress-activated p38 mitogen-activated
                     protein kinase induces low-density
                     lipoprotein receptor expression.
AUTHOR:              Mehta K D; Miller L
CORPORATE SOURCE:    Department of Biochemistry and Molecular Biology, College
                     of Medicine, University of Arkansas for Medical Sciences,
                     Little Rock 72205, USA.
SOURCE:              TRENDS IN CARDIOVASCULAR MEDICINE, (1999 Oct) 9 (7) 201-5.
                     Ref: 38
                     Journal code: 9108337. ISSN: 1050-1738.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
                     General Review; (REVIEW)
                     (REVIEW, TUTORIAL)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200008
ENTRY DATE:          Entered STN: 20000818
                     Last Updated on STN: 20000818
                     Entered Medline: 20000809
AB   We have recently shown that different signal transduction pathways
     initiated by a variety of agents converge on growth-responsive p42/44MAPK
     signaling cascade to induce low-density lipoprotein (LDL)
     receptor expression.  Our recent demonstration that
     stress-activated p38MAPK negatively regulates LDL
     receptor expression in an isoform-specific manner via modulation.
     of p42/44MAPK cascade represents a new dimension of complexity in the
     molecular communication that governs LDL receptor
     expression.  The suggested one-way communication between p38MAPK and
     p42/44MAPK provides a potential mechanism for fine-tuning cellular levels
     of cholesterol in response to a diverse set of environmental cues,
     including stress.  Cross talk between MAPKs opens new avenues
     toward understanding a variety of pathogenic processes; this makes them
     tempting targets for therapeutic interventions in cardiovascular diseases.

L17  ANSWER 2 OF 13     MEDLINE
ACCESSION NUMBER:    1999438160     MEDLINE
DOCUMENT NUMBER:     99438160   PubMed ID: 10508211
TITLE:               Critical role of p42/44(MAPK) activation in
                     anisomycin and hepatocyte growth factor-induced LDL
                     receptor expression: activation of
                     Raf-1/Mek-1/p42/44(MAPK) cascade alone is
                     sufficient to induce LDL receptor
                     expression.
AUTHOR:              Dhawan P; Bell A; Kumar A; Golden C; Mehta K D
CORPORATE SOURCE:    Department of Biochemistry and Molecular Biology, College
                     of Medicine, University of Arkansas for Medical Sciences,
                     4301 West Markham, Little Rock, AR 72205, USA.
CONTRACT NUMBER:     HL-51592-04 (NHLBI)
```

SOURCE: JOURNAL OF LIPID RESEARCH, (1999 Oct) 40 (10) 1911-9.
Journal code: 0376606. ISSN: 0022-2275.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20020420
Entered Medline: 19991223

AB The protein synthesis inhibitor anisomycin activates stress-related mitogen-activated protein kinases (**MAPKs**), namely, c-jun NH(2)-terminal kinase (p46/54(JNK)) and p38(**MAPK**) in mammalian cells. In this paper, we show that although exposure to anisomycin resulted in rapid and strong activation of p46/54(JNK) and p38(**MAPK**), with a delayed low level dual-phosphorylation of mitogen/extracellular protein kinase (p42/44(**MAPK**)), low density lipoprotein (**LDL**) **receptor** induction depends solely on the mild activation of p42/44(**MAPK**) signaling cascade in HepG2 cells. Unlike hepatocyte growth factor (HGF) which caused **LDL receptor** induction via rapid, strong, and Ras-dependent p42/44(**MAPK**) activation, anisomycin-induced p42/44(**MAPK**) activity and increased **LDL receptor** expression in a Ras-independent manner. Finally, we examined the role of the p42/44(**MAPK**) signaling cascade in **LDL receptor** induction by activating this kinase independently of anisomycin or HGF. By using estrogen-dependent human Raf-1 protein kinase in transient transfection assays, we show that the exclusive activation of the Raf-1/MEK-1/p42/44(**MAPK**) signaling cascade with antiestrogen ICI 182, 780 caused induction of **LDL receptor** expression to the same level as observed with either HGF or anisomycin. Consistent with the role of p42/44(**MAPK**), induction was strongly inhibited by pretreatment with the MEK-1/2 inhibitor PD98059.Our observation that anisomycin can use p42/44(**MAPK**) signaling cascade is a departure from established thinking, and the results presented shows that activation of the p42/44(**MAPK**) alone is sufficient to fully induce **LDL receptor** transcription.

L17 ANSWER 3 OF 13 MEDLINE
ACCESSION NUMBER: 1999321880 MEDLINE
DOCUMENT NUMBER: 99321880 PubMed ID: 10391894
TITLE: One-way cross-talk between p38(**MAPK**) and p42/44(**MAPK**). Inhibition of p38(**MAPK**) induces **low density lipoprotein receptor** expression through activation of the p42/44(**MAPK**) cascade.
AUTHOR: Singh R P; Dhawan P; Golden C; Kapoor G S; **Mehta K D**
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, USA.
CONTRACT NUMBER: HL-51592 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Jul 9) 274 (28) 19593-600.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990816
Last Updated on STN: 20000303

Entered Medline: 19990805

AB In this paper, we report that SB202190 alone, a specific inhibitor of p38(**MAPK**), induces low density lipoprotein (**LDL**) **receptor** expression (6-8-fold) in a sterol-sensitive manner in HepG2 cells. Consistent with this finding, selective activation of the p38(**MAPK**) signaling pathway by expression of MKK6b(E), a constitutive activator of p38(**MAPK**), significantly reduced **LDL receptor** promoter activity. Expression of the p38(**MAPK**) alpha-isoform had a similar effect, whereas expression of the p38(**MAPK**) betaII-isoform had no significant effect on **LDL receptor** promoter activity. SB202190-dependent increase in **LDL receptor** expression was accompanied by induction of p42/44(**MAPK**), and inhibition of this pathway completely prevented SB202190-induced **LDL receptor** expression, suggesting that p38(**MAPK**) negatively regulates the p42/44(**MAPK**) cascade and the responses mediated by this kinase. Cross-talk between these kinases appears to be one-way because modulation of p42/44(**MAPK**) activity did not affect p38(**MAPK**) activation by a variety of stress inducers. Taken together, these findings reveal a hitherto unrecognized one-way communication that exists between p38(**MAPK**) and p42/44(**MAPK**) and provide the first evidence that through the p42/44(**MAPK**) signaling cascade, the p38(**MAPK**) alpha-isoform negatively regulates **LDL receptor** expression, thus representing a novel mechanism of fine tuning cellular levels of cholesterol in response to a diverse set of environmental cues.

L17 ANSWER 4 OF 13 MEDLINE

ACCESSION NUMBER: 1998288318 MEDLINE
DOCUMENT NUMBER: 98288318 PubMed ID: 9624172
TITLE: Differential roles of extracellular signal-regulated kinase-1/2 and p38(**MAPK**) in interleukin-1beta- and tumor necrosis factor-alpha-induced **low density lipoprotein receptor** expression in HepG2 cells.
AUTHOR: Kumar A; Middleton A; Chambers T C; **Mehta K D**
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, USA.
CONTRACT NUMBER: HL-51592-04 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Jun 19) 273 (25) 15742-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980716
Last Updated on STN: 20000303
Entered Medline: 19980709

AB The inflammatory cytokines interleukin-1beta (IL-1beta) and tumor necrosis factor-alpha (TNF), elevated in inflammatory, malignant, and infectious diseases, induce low density lipoprotein (**LDL**) **receptor** transcription in HepG2 cells, and such an induction can account for hypocholesterolemia associated with these states. However, the signaling mechanisms of cytokine-mediated **LDL receptor** induction are largely unexplored. In the present studies, we examined the potential involvement of different mitogen-activated protein kinase (**MAPK**) pathways. Northern analysis demonstrated that IL-1beta or TNF significantly increased **LDL receptor** transcript in HepG2 cells, whereas expression of another tightly regulated

sterol-responsive squalene synthase gene was unaffected. IL-1beta treatment resulted in transient activation of three **MAPK** cascades, namely p46/54(JNK), p38(**MAPK**), and ERK-1/2, with maximal activation of 20-, 25-, and 3-fold, respectively, occurring 15-30 min after cytokine addition. PD98059, a specific inhibitor of **MAPK** kinase activity, inhibited IL-1beta-induced **LDL receptor** expression. In contrast, SB202190, a specific inhibitor of p38(**MAPK**), enhanced IL-1beta-induced **LDL receptor** expression, with a concomitant increase in ERK-1/2 activity. Similarly, TNF induced **LDL receptor** expression also required ERK-1/2 activation. Finally, sterols repressed IL-1beta induced receptor expression, without affecting ERK-1/2 activation. These results show that IL-1beta- or TNF-induced **LDL receptor** expression requires ERK-1/2 activation, that the p38(**MAPK**) pathway negatively regulates **LDL receptor** expression, and that sterols inhibit induction at a point downstream of ERK-1/2 in HepG2 cells.

L17 ANSWER 5 OF 13 MEDLINE
ACCESSION NUMBER: 1998052315 MEDLINE
DOCUMENT NUMBER: 98052315 PubMed ID: 9392422
TITLE: Phorbol ester-induced **low density lipoprotein receptor** gene expression in HepG2 cells involves protein kinase C-mediated p42/44 MAP kinase activation.
AUTHOR: Kumar A; Chambers T C; Cloud-Heflin B A; **Mehta K D**
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock 72205-7199, USA.
CONTRACT NUMBER: HL-51592-04 (NHLBI)
SOURCE: JOURNAL OF LIPID RESEARCH, (1997 Nov) 38 (11) 2240-8. Journal code: 0376606. ISSN: 0022-2275.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980217
Last Updated on STN: 20000303
Entered Medline: 19980130

AB The signaling pathway involved in low density lipoprotein (**LDL**) **receptor** gene expression induced by the phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA) was investigated in the human hepatoma HepG2 cell line. Treatment of HepG2 cells with 100 nM TPA resulted in an approximately 20-fold increase in **LDL receptor** mRNA level, as determined by RT-PCR, which peaked at 2-4 h of treatment and subsequently declined. The protein kinase C (PKC) inhibitors calphostin C and staurosporine prevented TPA-mediated **LDL receptor** mRNA induction. In contrast, TPA did not affect squalene synthase mRNA expression. Immunoblotting of cell extracts with isozyme-specific PKC antibodies revealed that HepG2 cells expressed PKC alpha, which was mainly cytosolic, and PKC beta, PK epsilon, and PKC zeta, all of which were present in both the cytosolic and particulate fractions. Treatment of HepG2 cells with 100 nM TPA resulted in translocation of cytosolic PKC alpha to the particulate fraction, with a maximum at 30 min-2 h of treatment, but was without effect on the subcellular distribution of the other isozymes. TPA treatment also led to activation of the mitogen-activated protein kinase (**MAPK**) ERK cascade. The specific **MAPK** pathway inhibitor PD98059 blocked TPA-induced ERK activation. Furthermore, pretreatment of cells with PD98059 inhibited TPA-induced **LDL receptor** mRNA induction. Moreover, pretreatment of cells with calphostin C inhibited

TPA-mediated ERK activation and **LDL receptor** mRNA induction in a dose-dependent fashion. Based on a close kinetic correlation between PKC alpha translocation and ERK activation, and the effects of specific inhibitors, these findings suggest that translocation/activation of PKC alpha, and subsequent activation of the Raf-1/MEK/ERK **MAPK** cascade, represent key events in the transcriptional induction of **LDL receptor** gene by TPA in HepG2 cells.

L17 ANSWER 6 OF 13 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002279144 EMBASE
TITLE: Activation of Raf-1/MEK-1/2/p42/44(**MAPK**) cascade alone is sufficient to uncouple **LDL receptor** expression from cell growth.
AUTHOR: Kapoor G.S.; Atkins B.A.; **Mehta K.D.**
CORPORATE SOURCE: K.D. Mehta, Dept. of Molecular/Cell. Biochemist., Ohio State Univ. College Medicine, 464 Hamilton Hall, 1645 Neil Avenue, Columbus, OH 43210, United States. mehta.80@osu.edu
SOURCE: Molecular and Cellular Biochemistry, (2002) 236/1-2 (13-22).
Refs: 36
ISSN: 0300-8177 CODEN: MCBIB8
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Our previous observation that induction of low density lipoprotein (**LDL**) **receptor** expression by a variety of extracellular signals is blocked by PD98059, a specific mitogen-activated protein kinase kinase inhibitor, led to the suggestion that the growth-responsive p42/44(**MAPK**) cascade plays a critical role in regulating **LDL receptor** transcription. To analyze the specific contribution of the p42/44(**MAPK**) cascade in regulating cell growth and **LDL receptor** induction, we established a HepG2-derived cell line that stably expresses an inducible form of oncogenic human Raf-1 kinase. Using this system, we provide direct evidence that specific activation of this cascade alone is not only required but is sufficient to fully induce **LDL receptor** expression. Interestingly, degree of p42/44(**MAPK**) activation determines the extent of **LDL receptor** induction. However, activation of p42/44(**MAPK**) in the above cells led to the inhibition of DNA synthesis, caused growth arrest, decrease in cyclin A and upregulation of p21(Cip) expression in a time-dependent manner. These results suggest that each of these two processes can be regulated independently of each other in response to p42/44(**MAPK**) activation. Thus, extent of p42/44(**MAPK**) activation may be important in transducing divergent cellular responses in human cells with implications for altered signaling resulting in hypercholesterolemia.

L17 ANSWER 7 OF 13 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002274870 EMBASE
TITLE: Role of mitogen-activated protein kinases and protein kinase C in regulating **low-density lipoprotein receptor** expression.
AUTHOR: **Mehta K.D.**
CORPORATE SOURCE: K.D. Mehta, Department of Cellular Biochemistry, Ohio State Univ. College of Medicine, Columbus, OH 43210, United States. mehta.80@osu.edu
SOURCE: Gene Expression, (2002) 10/4 (153-164).
Refs: 95
ISSN: 1052-2166 CODEN: GEEXEJ

COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The cell signaling pathways that culminate in induction of low-density lipoprotein (**LDL**) **receptor** transcription in response to a variety of extracellular and intracellular signals are beginning to be defined. Evidence is accumulating that **LDL receptor** transcription is under complex regulation and that a major pathway of induction by cytokines, growth factors, anisomycin, and phorbol esters involves the extracellular/mitogen-activated protein kinase (p42/44(**MAPK**)) cascade. In fact, degree p42/44(**MAPK**) activation determines the extent of **LDL receptor** induction. The suppression of **LDL receptor** expression by stress-activated p38(**MAPK**) via p42/44(**MAPK**) provides a potential mechanism for stress-induced hypercholesterolemia observed in humans and animals. Moreover, endogenous signals such as cholesterol regulate **LDL receptor** transcription through a different signaling cascade involving protein kinase C.epsilon. isoform (PKC.epsilon.). The ability of cholesterol to directly bind PKC.epsilon. in an isoform-specific manner strongly supports its role in sensing the cellular cholesterol levels. The emerging picture from the above studies is that regulation of **LDL receptor** transcription results from the activity of a number of interlinked regulatory molecules and pathways, rather than from a single linear series of events. These studies will provide the necessary framework for understanding differential responses within human populations to atherosclerosis following high-fat/cholesterol diet. This information may also provide new strategies to modulate specific gene expression with the hope to develop novel therapies for the treatment of hypercholesterolemia.

L17 ANSWER 8 OF 13 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002179351 EMBASE
TITLE: Critical role of diacylglycerol- and phospholipid-regulated protein kinase C.epsilon. in Induction of **low-density lipoprotein receptor** transcription in response to depletion of cholesterol.
AUTHOR: **Mehta K.D.**; Radominska-Pandya A.; Kapoor G.S.; Dave B.; Atkins B.A.
CORPORATE SOURCE: K.D. Mehta, Department of Cellular Biochemistry, Ohio State Univ. College of Medicine, 464 Hamilton Hall, 1645 Neil Ave., Columbus, OH 43210, United States. mehta.80@osu.edu
SOURCE: Molecular and Cellular Biology, (2002) 22/11 (3783-3793). Refs: 58
ISSN: 0270-7306 CODEN: MCEBD4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Induction of low-density lipoprotein (**LDL**) **receptor** transcription in response to depletion of cellular sterols in animal cells is well established. The intracellular signal or signals involved in regulating this process, however, remain unknown. Using a specific inhibitor of protein kinase C (PKC), calphostin C, we show the requirement of this kinase in the induction process in human hepatoma HepG2 cells. Overexpression of PKC.epsilon., but not PKC.alpha., -.gamma., -.delta., or .zeta. was found to dramatically induce (approximately 18-fold) **LDL receptor** promoter activity. Interestingly, PKC.epsilon.-mediated induction was found to be sterol resistant. To further establish that PKC.epsilon. is involved in the sterol regulation

of **LDL receptor** gene transcription, endogenous PKC.epsilon. was specifically inhibited by transfection with antisense PKC.epsilon. phosphorothionate oligonucleotides. Antisense treatment decreased endogenous PKC.epsilon. protein levels and completely blocked induction of **LDL receptor** transcription following sterol depletion. PKC.epsilon.-induced **LDL receptor** transcription is independent of the extracellular signal-regulated kinase 1 and 2 (p42/44(**MAPK**)) cascade, because the MEK-1/2 inhibitor, PD98059 did not inhibit, even though it blocked p42/44(**MAPK**) activation. Finally, photoaffinity labeling studies showed an isoform-specific interaction between PKC.epsilon. and sterols, suggesting that sterols may directly modulate its function by hampering binding of activators. This was confirmed by PKC activity assays. Altogether, these results define a novel signaling pathway leading to induction of **LDL receptor** transcription following sterol depletion, and a model is proposed to account for a new function for PKC.epsilon. as part of a sterol-sensitive signal transduction pathway in hepatic cells.

L17 ANSWER 9 OF 13 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000226341 EMBASE
TITLE: Inhibition of stress-activated p38 mitogen-activated protein kinase induces **low-density lipoprotein receptor** expression.
AUTHOR: **Mehta K.D.**; Miller L.
CORPORATE SOURCE: K.D. Mehta, Dept. Biochemistry/Molecular Biology, College of Medicine, University of Arkansas, 4301 West Markham, Little Rock, AR 72205, United States
SOURCE: Trends in Cardiovascular Medicine, (2000) 9/7 (201-205). Refs: 38
ISSN: 1050-1738 CODEN: TCMDEQ
PUBLISHER IDENT.: S 1050-1738(00)00021-9
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
025 Hematology
029 Clinical Biochemistry
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We have recently shown that different signal transduction pathways initiated by a variety of agents converge on growth-responsive p42/44(**MAPK**) signaling cascade to induce low-density lipoprotein (**LDL**) **receptor** expression. Our recent demonstration that stress-activated p38(**MAPK**) negatively regulates **LDL receptor** expression in an isoform-specific manner via modulation of p42/44(**MAPK**) cascade represents a new dimension of complexity in the molecular communication that governs **LDL receptor** expression. The suggested one-way communication between p38(**MAPK**) and p42/44(**MAPK**) provides a potential mechanism for fine-tuning cellular levels of cholesterol in response to a diverse set of environmental cues, including stress. Cross talk between **MAPKs** opens new avenues toward understanding a variety of pathogenic processes; this makes them tempting targets for therapeutic interventions in cardiovascular diseases. Copyright (C) 1999 Elsevier Science Inc.

L17 ANSWER 10 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2003:186246 BIOSIS
DOCUMENT NUMBER: PREV200300186246
TITLE: Requirement of pp90RSK and protein kinase C in p42/44MAPK-induced **LDL receptor** transcription.

AUTHOR(S): **Mehta, K. D. (1)**; Atkins, B. (1); Kapoor, G. S. (1)
CORPORATE SOURCE: (1) Molecular and Cellular Biochemistry, College of Medicine, Ohio State University, Columbus, OH, USA USA
SOURCE: Molecular Biology of the Cell, (Nov. 2002, 2002) Vol. 13, No. Supplement, pp. 17a. print.
Meeting Info.: 42nd Annual Meeting of the American Society for Cell Biology San Francisco, CA, USA December 14-18, 2002 American Society for Cell Biology
. ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L17 ANSWER 11 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:167257 BIOSIS
DOCUMENT NUMBER: PREV199900167257
TITLE: **LDL receptor** expression is regulated positively by P42/44MAPK pathway in hepatic cells.
AUTHOR(S): Dhawan, P. (1); McMahon, M.; **Mehta, K. D. (1)**
CORPORATE SOURCE: (1) Dep. Biochemistry Molecular Biology, Univ. Ark. Med. Sciencdes 4301, West Markham St., Littlerock, AR 72205 USA
SOURCE: FASEB Journal, (March 12, 1999) Vol. 13, No. 4 PART 1, pp. A194.
Meeting Info.: Annual Meeting of the Professional Research Scientists for Experimental Biology 99 Washington, D.C., USA April 17-21, 1999
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English

L17 ANSWER 12 OF 13 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 2003:239423 SCISEARCH
THE GENUINE ARTICLE: 653XF
TITLE: pp90(RSK)- and protein kinase C-dependent pathway regulates p42/44(**MAPK**)-induced **LDL receptor** transcription in HepG2 cells
AUTHOR: Kapoor G S; Golden C; Atkins B; **Mehta K D (Reprint)**
CORPORATE SOURCE: Ohio State Univ, Coll Med & Publ Hlth, Dept Mol & Cellular Biochem, 464 Hamilton Hall, 1645 Neil Ave, Columbus, OH 43210 USA (Reprint); Ohio State Univ, Coll Med & Publ Hlth, Dept Mol & Cellular Biochem, Columbus, OH 43210 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF LIPID RESEARCH, (MAR 2003) Vol. 44, No. 3, pp. 584-593.
Publisher: LIPID RESEARCH INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA.
ISSN: 0022-2275.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 46
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have previously shown that different extracellular stimuli require signaling through the Raf/MEK/p42/44(**MAPK**) cascade to induce **LDL receptor** expression. The present studies were designed to delineate the molecular mechanisms underlying p42/44(**MAPK**)-induced **LDL receptor** transcription in HepG2-DeltaRaf-1:ER cells, a modified HepG2 cell line in which the Raf-1/MEK/p42/44(**MAPK**) cascade can be specifically activated by anti-estradiol ICI182,780 in an agonist-specific manner. Using these cells, we show that: a) **LDL receptor** induction was reduced in reporter constructs containing mutation in either Sp1 or

sterol-regulatory element-1 (SRE-1) sites, whereas inactivation of both sites abolished the induction; b) E1A, which inhibits CREB binding protein (CBP), a common activator of SRE-1 binding protein and Sp1, strongly repressed the induction; c) intracellular inhibition of the 90 kDa ribosomal S6 kinase (pp90(RSK)) cascade reduced **LDL receptor** induction; d) highly selective protein kinase C (PKC) inhibitors effectively abrogated the induction without affecting activation of pp90RSK; and e) overexpression of PKCbeta significantly induced **LDL receptor** promoter activity. Taken together, these results demonstrate that pp90(RSK) and PKCbeta are downstream effectors and Sp1, SRE-1 binding protein, and CBP are part of the transcriptional complex resulting in induction of **LDL receptor** expression in response to activation of the Raf/MEK/p42/44(**MAPK**) cascade. These findings identify for the first time a role for PKC(3 in determining the specificity of p42/44(**MAPK**) signaling by participating with pp90RSK in regulating gene expression.

L17 ANSWER 13 OF 13 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 1999:808341 SCISEARCH
THE GENUINE ARTICLE: 226QW
TITLE: **Ldl receptor** expression is regulated positively by p42/44(**MAPK**) pathway in hepatic cells.
AUTHOR: Dhawan P (Reprint); McMahon M; **Mehta K D**
CORPORATE SOURCE: UNIV ARKANSAS MED SCI, DEPT BIOCHEM & MOL BIOL, LITTLE ROCK, AR 72205; UNIV CALIF SAN FRANCISCO, CANC RES INST, SAN FRANCISCO, CA 94145
COUNTRY OF AUTHOR: USA
SOURCE: FASEB JOURNAL, (12 MAR 1999) Vol. 13, No. 4, Part 1, Supp. [S], pp. A194-A194.
Publisher: FEDERATION AMER SOC EXP BIOL, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998.
ISSN: 0892-6638.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 0

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(FILE 'HOME' ENTERED AT 11:22:37 ON 02 MAY 2003)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 11:23:02 ON 02 MAY 2003

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L1        21973 S "LDL RECEPTOR?"
L2       224249 S LOW (A) DENSITY
L3       156053 S L2 (A) LIPOPROTEIN
L4        17154 S L3 (A)RECEPTOR?
L5        30924 S L1 OR L4
L6          154 S "P42/44MAPK"
L7          154 S P42(W)44MAPK
L8          154 S L6 OR L7
L9           21 S L8 AND L5
L10          11 DUP REM L9 (10 DUPLICATES REMOVED)
                E MEHTA K D/AU
L11         122 S E3
L12          58 S L5 AND L11
L13           4 S L7 AND L12
L14           4 DUP REM L13 (0 DUPLICATES REMOVED)
L15           4 S L8 AND L11
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L16 21 DUP REM L12 (37 DUPLICATES REMOVED)
L17 13 S L16 AND MAPK

	L #	Hits	Search Text
1	L1	0	"LDL receptor$2"
2	L2	65059	"low density"
3	L3	12120	lipoprotein$2
4	L4	4703	l2 same l3
5	L5	1221	"p42/44mapk" or "erk##"
6	L6	3	l4 same l5
7	L7	821	mehta.in.
8	L8	2	l4 and l7
9	L9	3	l7 and l5

	~~Issue Date~~	Pages	Document ID	Title
1	20020627	24	US 20020082192 A1	Induction of LDL receptor expression by extracellular-signal regulated kinase, ERK-1/2
2	20020124	57	US 20020009730 A1	Human stress array
3	20000215	62	US 6025194 A	Nucleic acid sequence of senescence asssociated gene

	~~Issue Date~~	Pages	Document ID	Title
1	20020924	88	US 6455593 B1	Method of dynamic retardation of cell cycle kinetics to potentiate cell damage
2	20020627	24	US 20020082192 A1	Induction of LDL receptor expression by extracellular-signal regulated kinase, ERK-1/2
3	20010814	92	US 6274576 B1	Method of dynamic retardation of cell cycle kinetics to potentiate cell damage